Fungal infections and masses in central nervous system: Diagnosis and management

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Introduction

Fungi are saphrophytes

- Yeast - candida, cryptococcus , trichosporon
- Filamentous – rhizopus, rhizomucor, mucor
- Dimorphic Fungi- blastomyces , histoplasma, coccidoides , paracoccidoides

INFECTIVE PHASES OF FUNGI

ORGANISM	CLASSIFICATION	PATHOGENIC PHASE
PATHOGENIC		
BLASTOMYCES	DIMORPHIC	YEAST
COCCIDOIDES	DIMORPHIC	SPHERULES
HISTOPLASMA	DIMORPHIC	YEAST
PARACOCCIDOIDES	DIMORPHIC	YEAST
OPPORTUNISTIC		
ASPERGILLUS	MOULD	HYPHAL
CANDIDA	YEAST	YEAST
ZYGOMYCETES	MOULD	HYPHAL
CRYPTOCOCCUS	YEAST	YEAST

Introduction

- Commonly seen in tropical countries
- Incidence is increasing world wide

  -Immune suppression

  -Broad spectrum antibiotic

  -Steroids

  -Drug abuse

  -AIDS , malignancy

  -International travel

- Mode of infection
  - -Hematogenous spread
  - -Direct inoculation
  - -Adjacent contiguous spread

Pathology

- Depends on size forms

  a. Small size - yeast enter microcirculation
  micro-abscess, meningitis

  b. Larger hyphal forms-invade vasculature
  cause infarcts

  c. Host immune response

CNS MANIFESTATIONS

- Meningitis
- Meningoencephalitis
- Space occupying lesion
- Hemorrhage, infarction,
- Myelopathy

CLINICAL FEATURES

- Meningeal syndromes- headache, nausea, vomiting, neck stiffness , fever, cranial nerve paresis, focal signs due to arteritis
- Meningitis is subacute/ chronic
- Meningoencephalitis
- Hydrocephalus

Clinical features

- Space occupying lesions-
  granulomas
  abscesses
- Spinal cord compression
- Rhinocerebral syndromes
- Skull base syndromes
- Stroke syndromes

Table 1: Fungal infections of the CNS – clinical syndromes

Fungal infection	Meningitis	Intracranial mass lesions	Skull-base syndrome	Rhinocerebral form	Stroke syndrome	Spinal syndrome
Aspergillosis	+	++	+++	+	+	+
Zygomycosis	±	++	-	+++	+	-
Cryptococosis	+++	+	-	-	+	+
Pheohyphomycosis	+	+++	-	-	-	-
Candidiasis	+	-	-	-	+	-
Penicilliosis	+	-	-	-	-	+

Table 2: Fungal infections of the CNS – skull-base syndromes
Orbital apex syndrome
Cavernous sinus syndrome
Proptosis with or without ocular palsy
Polyneuritis cranialis
Orbito-cranial syndromes

High index of suspicion

Table 3: Diagnosis of fungal infections of the CNS
Immunocompromised host and diabetes mellitus
HIV infection
Transplant patient
Prosthetic valves
Paranasal sinus infection

INVESTIGATIONS

Routine

CSF proteins, sugar

-Cell examination

-Biochemical- count

-Cytological examination- India ink

-Cultures

-Immunoassay/ PCR

Investigations

Blood cultures

Imaging in CNS

MRI

CT SCAN

Biopsies

Evidence of infection elsewhere

ASPERGILLUS GRANULOMA

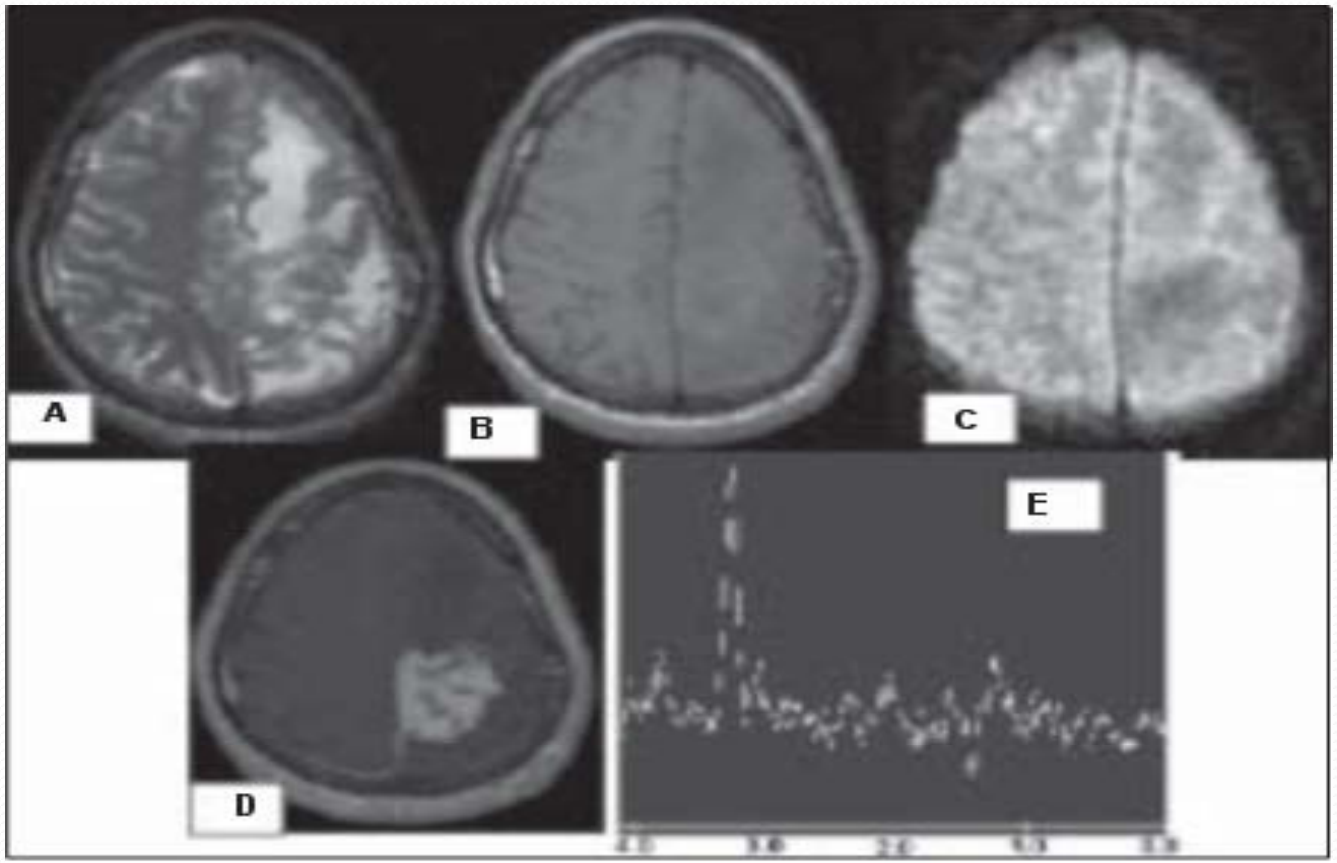


Figure 1: *Aspergillus* granuloma. Axial T2WI (A) showing a heterogeneous intensity lesion with surrounding hyperintensity in the left parietal region. Lesion is isointense on T1WI (B) and hypointense on DWI (C). Post-contrast image (D) shows intense enhancement of the mass lesion. PMRS (E) shows lactate (1.3 ppm) along with choline (3.2 ppm). Culture of the tissue was positive for *Aspergillus flavus*

RHINOCEREBRAL ASPERGILLOSIS

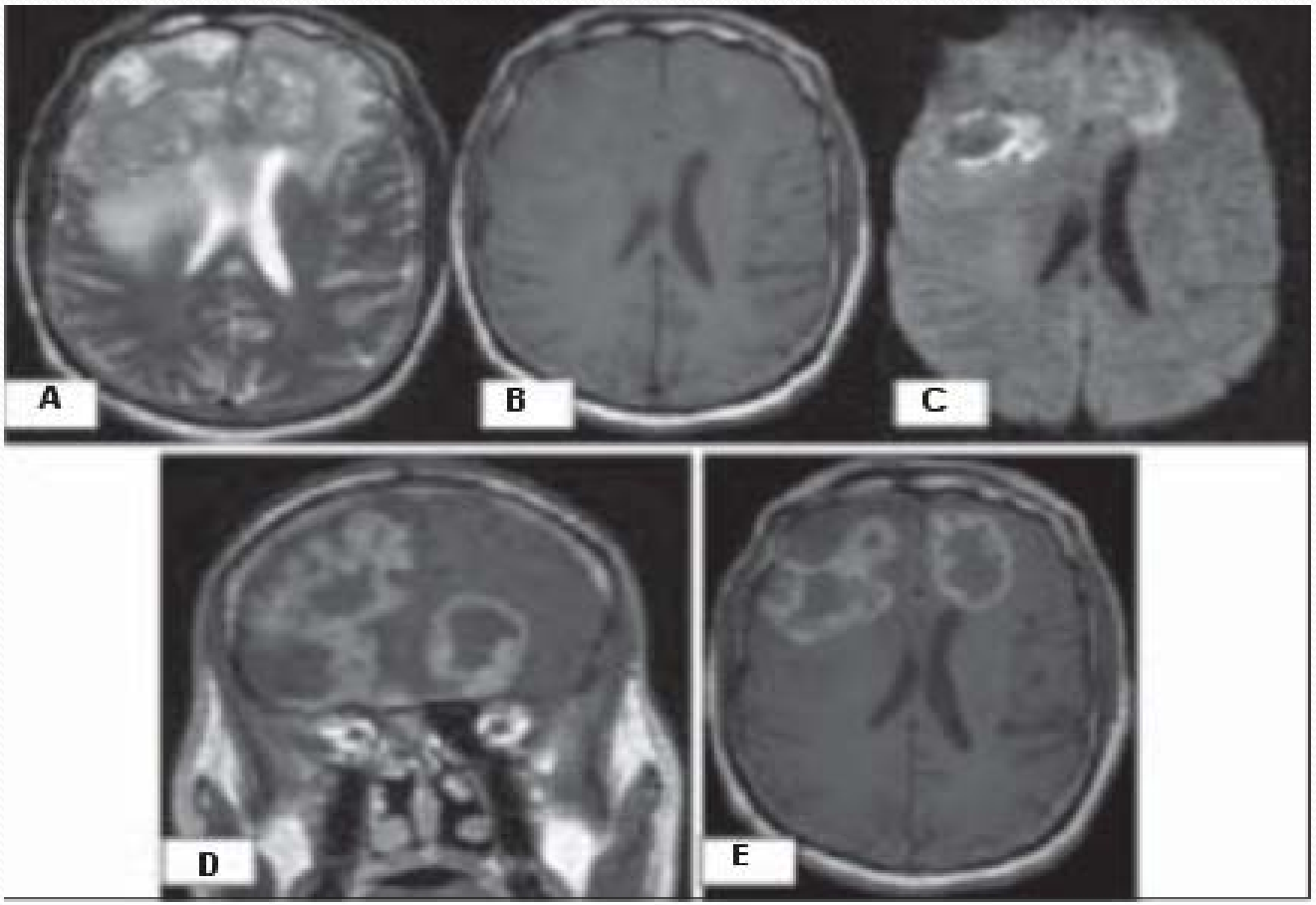


Figure 3: Rhinocerebral aspergillosis in an immunocompromised patient. Axial T2WI (A) showing heterogeneous intensity lesions with surrounding edema in bilateral frontal lobes. Lesions are iso to hyperintense on T1WI (B) and show mixed intensity on DWI (C). On post-contrast coronal (D) and axial (E) T1WI, lesions show heterogeneous peripheral enhancement with enhancing adjacent dura and involvement of ethmoid sinuses. Culture of the nasal scrapings grew *Aspergillus flavus*

RHINOCEREBRAL CANDIDIASIS

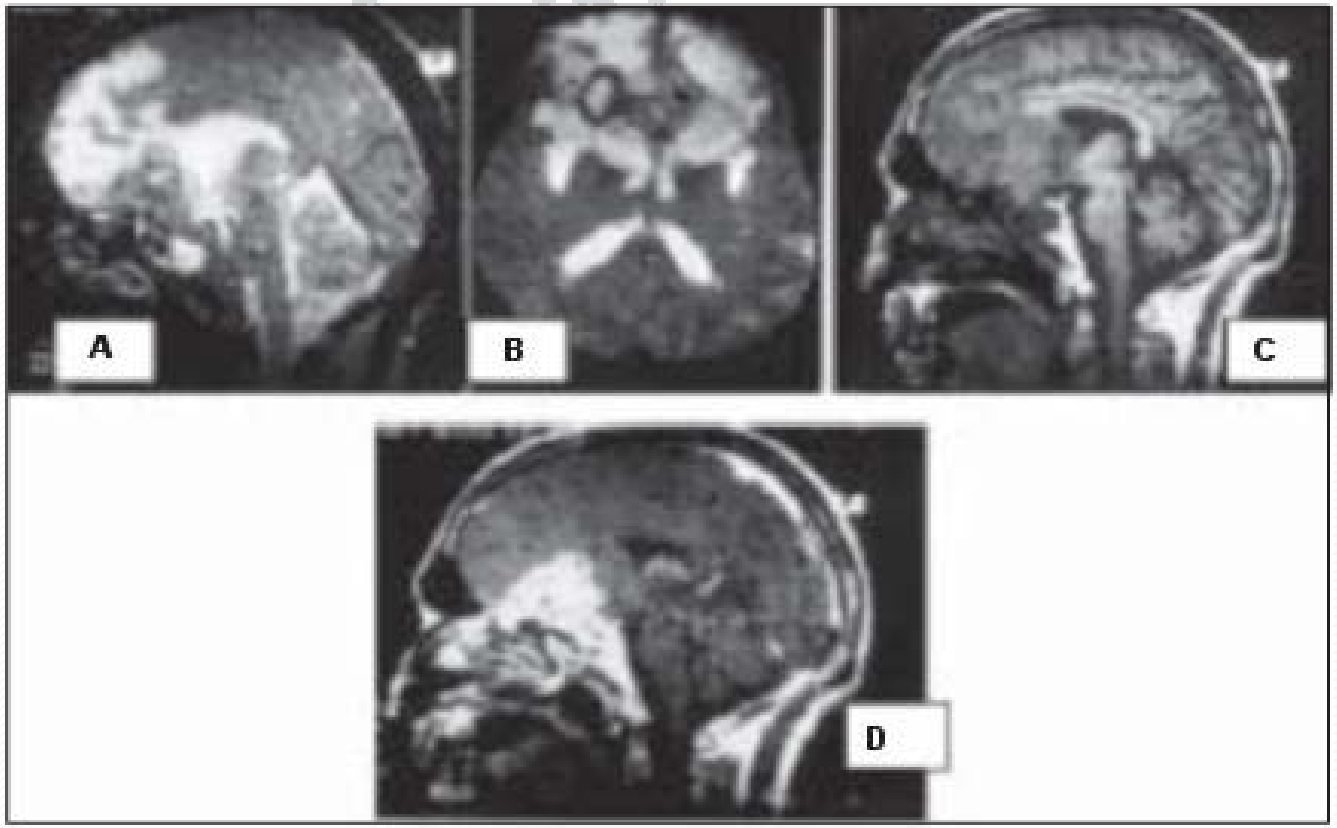
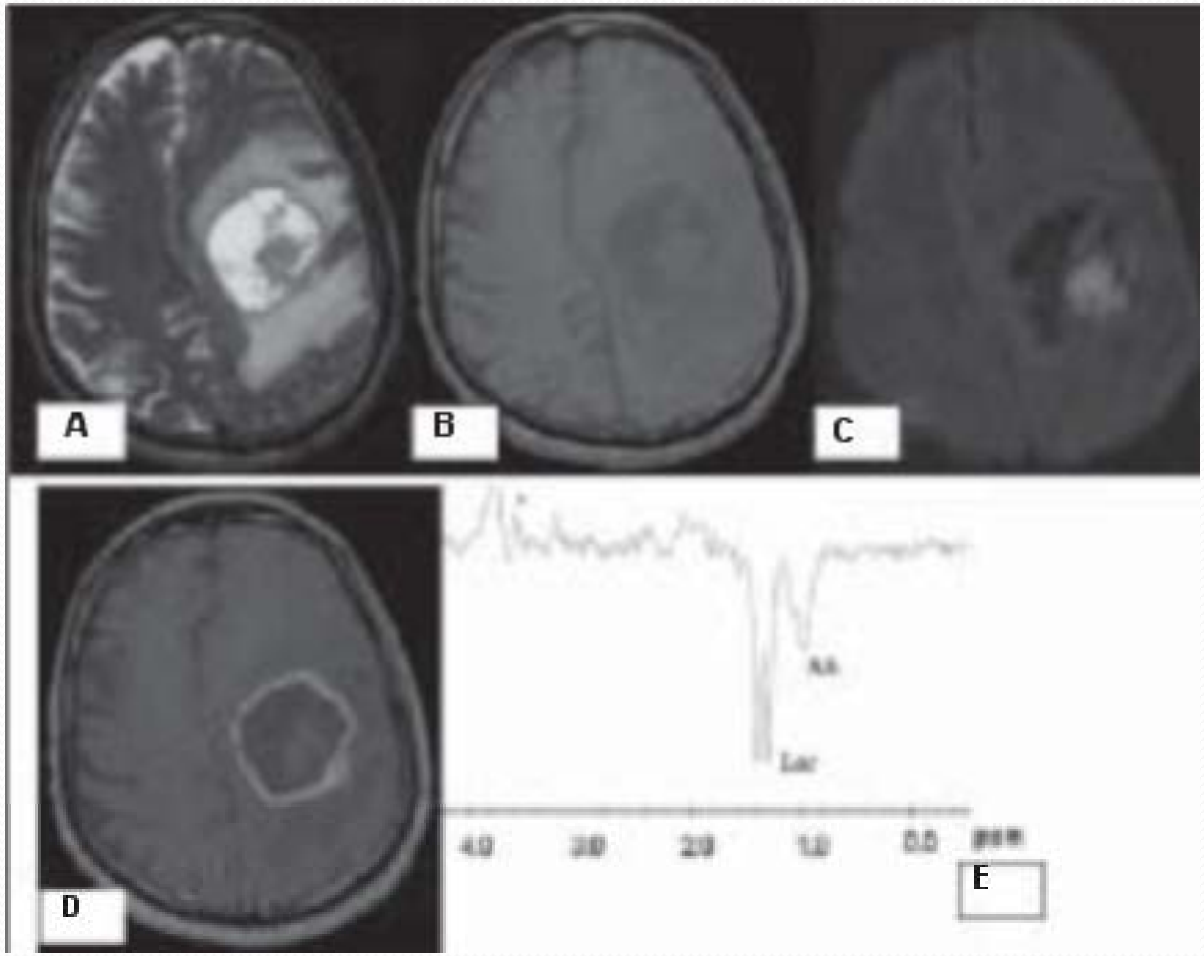


Figure 8: Rhinocerebral candidiasis. Sagittal T2WI (A) shows mixed intensity area in the basal frontal region with edema. Axial T2WI (B) shows multiple hyperintense areas with hypointense rims in the bilateral frontal lobes. Sagittal T1WI (C) shows the lesion to be isointense to gray matter. Post-contrast T1WI (D) shows heterogeneous enhancement of the lesion along with enhancing sphenoid and ethmoid sinuses. Pus culture from the brain grew *Candida albicans*

Fungal abscess



CRYPTOCOCCUS MENINGITIS

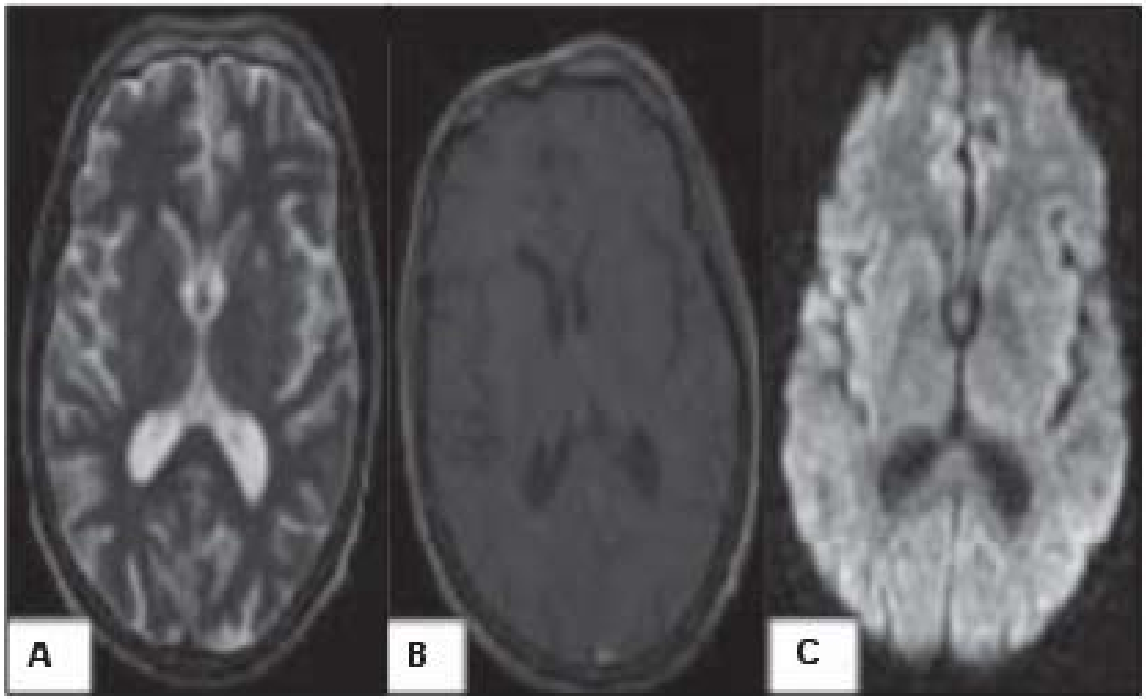


Figure 4: Cryptococcosis with dilated Virchow-Robin spaces in an immunocompromised patient. T2WI (A) shows multiple bilateral basal ganglia hyperintensities, which do not reveal any enhancement on post-contrast T1WI (B). Lesions show no restriction on DWI (C). CSF culture showed *Cryptococcus neoformans*

Treatment

- Nonspecific measures
  - Raised ICT – mannitol, frusemide
- Antifungal agents
- Surgical management
  Biopsy
  surgical excision
  -abscess drainage
  -insertion of ommaya chamber
  Shunt

Management of fungal intracranial fungal masses

Most commonly- Aspergillus sp

Divided into

a. Rhinocerebral /sinocranial

b. primary intracranial- 1. extra axial

2.intra axial

frontal lobes most commonly involved

fungal aneurysms – very rare

Management of fungal intracranial fungal masses

- Differential diagnosis- Tuberculoma, Lymphoma, Gliomas, Soft tissue malignancy

  Intracerebral – soft, suckable with pockets of pus

  Rhinocerebral- firm fibrous

Surgical management

- stereotactic biopsy/aspiration- deep seated lesions/ eloquent area, multiple lesions, frail patient
- Craniotomy – for easily accessible areas

PNS lesion- otolaryngorhinological surgery (FESS)

Shunt surgery

Endovascular coiling for fungal aneurysms

Antifungal therapy

Cryptococcus

Soil enriched pigeon droppings

Route of entry- respiratory system

affects RE system

Basal meningitis, Meningoencephalitis,

Granulomas and cysts- subependymal regions of thalamus and basal ganglia- single or grouped in jelly like mass

Spinal cryptococcosis- mass lesions, spinal arachanoiditis

Cerebrospinal fluid with *C neoformans*, India ink stain. Budding yeast indicated by arrow.

CRYPTOCOCCUS PSEUDOCYST

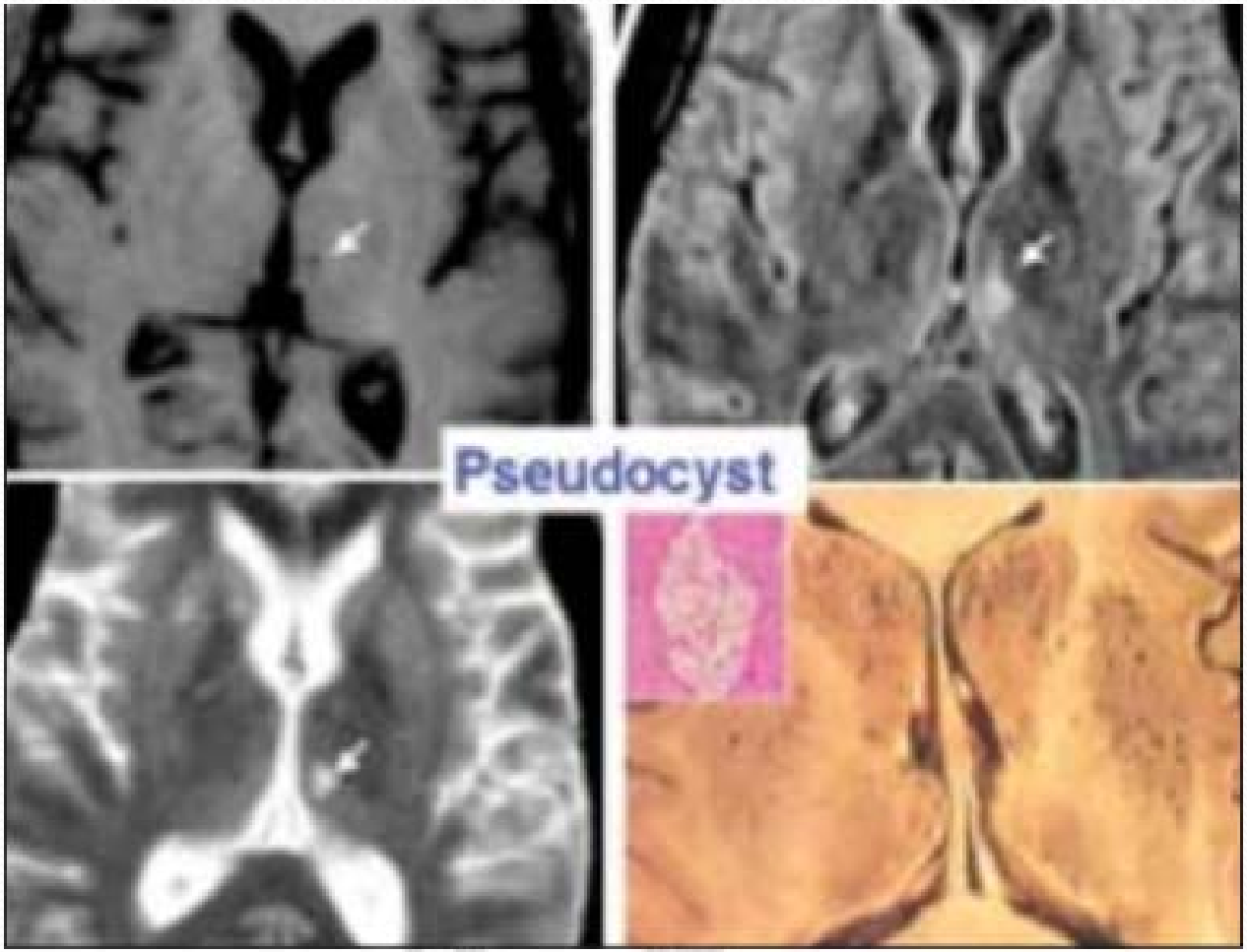


Figure 5: MRI demonstrating Pseudocyst formation

- Treatment of Cryptococcus (immunocompetent)

  Amphotericin B -0.7-1mg/kg/d +

  5-flucytosine 100mg/kg/d for 6-10 weeks

  OR

  Amphotericin B -0.7-1mg/kg/d +

  5-Flucytosine -100mg/kg/d for 2 weeks

  Fluconazole -400mg/d for 10 weeks can be continued for 6-12 months

Cryptococcosis: Treatment

- Preferred: (immunocompromised)
  - Induction (≥2 weeks):
    - Amphotericin B 0.7 mg/kg IV + flucytosine 25 mg/kg PO QID
    - Lipid formulation amphotericin B 4-6 mg/kg IV + flucytosine 25 mg/kg PO QID
  - Consolidation (8 weeks):
    - Fluconazole 400 mg PO
  - Chronic maintenance: fluconazole 200 mg PO QD

Cryptococcosis: Treatment (3)

- Flucytosine increases rate of CSF sterilization during induction therapy
- Consolidation therapy should not be started until ≥2 weeks of successful induction therapy:
  - Significant clinical improvement
  - Negative CSF culture on repeat lumbar puncture
- Fluconazole more effective than itraconazole for consolidation therapy

Cryptococcosis: Preventing Recurrence

- Secondary prophylaxis:
  - Lifelong suppressive treatment (after completion of initial therapy), unless immune reconstitution on ART
  - Preferred: fluconazole 200 mg /d
- Consider discontinuing maintenance therapy in asymptomatic patients on ART with sustained increase in CD_4 count to >200 cells/μL for ≥6 months
- Restart maintenance therapy if CD_4 count decreases to <200 cells/μL

Prognostic factors

- Cryptococcus
  - Positive india ink test
  - High opening pressure
  - Low CSF leucocyte
  - Extraneural cryptococcosis
  - Absent antibody
  - Initial CSF/serum cryptococcal titre 1:32
  - Corticosteroid

Aspergillosis

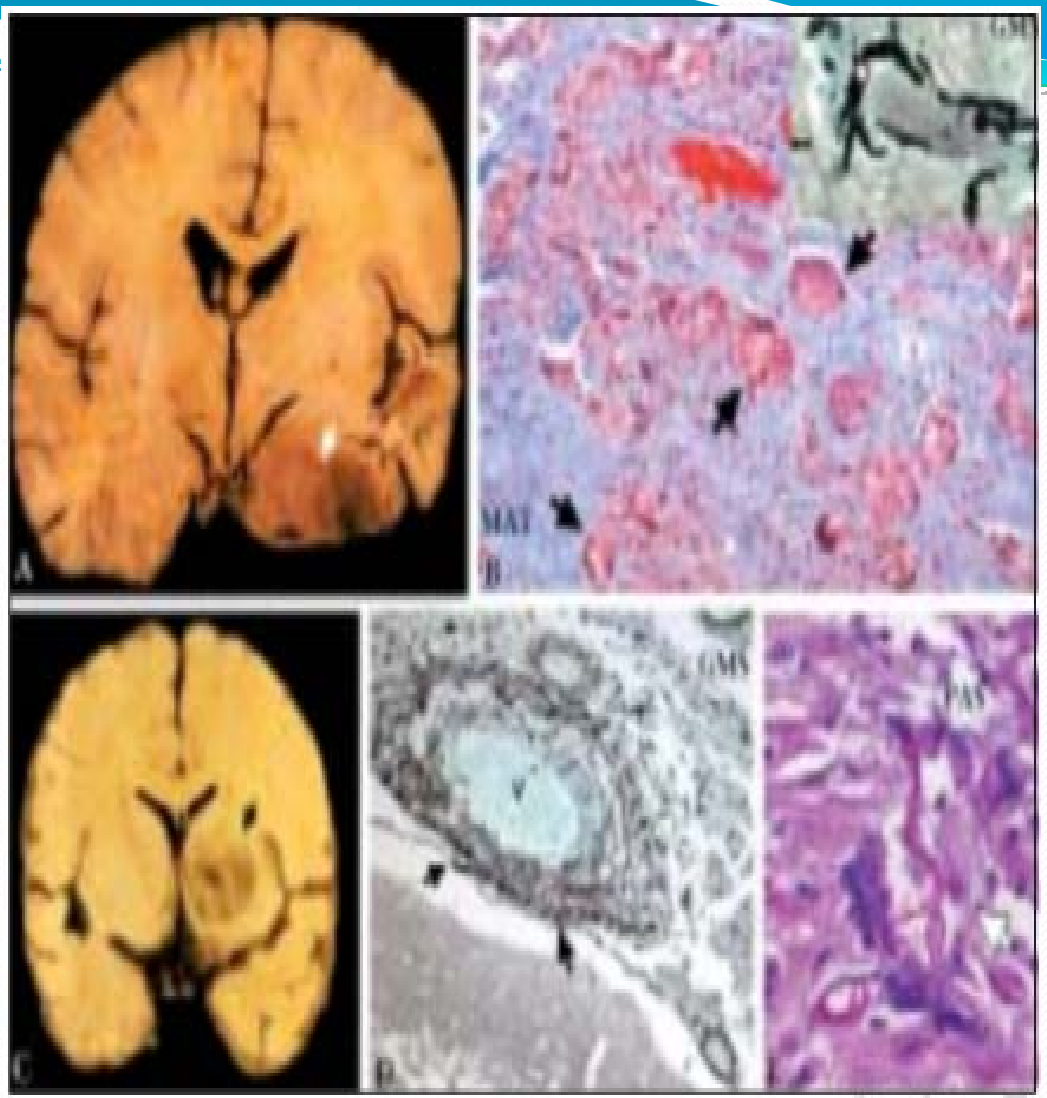
- Saprophyte in soil

  Hematogenous spread from GI tract/ Pulmonary

  High affinity to blood vessels

  Abscesses or Granulomas in CNS

  Treatment consists of surgery + antifungal



Basitemporal aspergillosis

Aspergillosis: Treatment

- Preferred: Voriconazole -6 mg/kg IV Q12H for 1 day, then 4 mg/kg IV Q12H until clinical response, then 200 mg PO Q12H
  - Not well studied in HIV-infected patients; significant interactions with protease inhibitors and efavirenz
- Alternative:
  - Amphotericin B 1 mg/kg IV/d or amphotericin B lipid formulation 5 mg/kg IV /d
  - Caspofungin 70 mg IV for 1, then 50 mg IV /d
  - Posaconazole 400 mg PO BID

Mucormycosis

- Rhizopus, rhizomucor and absidia

CNS -entry is by direct extension through paranasal sinuses along nerves, blood vessels andcartilage

Periorbital pain

Nasal discharge

Poorly controlled diabetic

Black necrotic mass

External opthalmoplegia and vision loss

- Diagnosis –biopsy

  surgical excision + antifungal therapy such as amphotericin- b

Candidiasis

- Gut commensal

  Through blood to CNS

  Immunosuppressed ,

  iv access,

  neutropenic patients,

  parenteral nutrition

  neurosurgical procedures

Small intraparenchymal micro abscesses in anterior and middle cerebral territory

Prognostic factors

- Candidal meningitis

  diagnosis delay >2 weeks

  CSF glucose <35mg/dl

  raised ICT

  focal deficits

Blastomycosis

- Inhalation of airborne spores
- Spread to CNS via hematogenous route

  or bony involvement , vertebrae are commonly involved
- Mimics tuberculosis of spine
- Treatment

surgery + antifungal treatment

coccidiodomycosis

- Soil saprophyte
- Route of entry of spore- lung

  chronic meningitis , granulomas in basal meninges mimicking tuberculous meningitis

  infects vertebral bodies
- Diagnosis by- subcutaneous nodules, csf antibodies, biopsy
- Treatment- amphotericin b or azoles

Nocardiosis

- Not a true fungi
- Soil saprophyte
- route of entry- lung/skin
- CNS-abscesses, granulomas, meningitis
- Treatment- sulphonamides

Antifungal drugs

- **Polyenes-** Amphotericin B
- **Azoles-** ketocanozole, voriconazole, fluconazole, itraconazole
- **Heterocyclic** – Griseofulvin
- **Antimetabolite-** Flucytosine
- **Echinocandins** – Capsofungin

- Polyenes
  - Fungicidal
  - Increasing the permeability of the cell membrane by targeting ergosterol in the membrane
  - Include nystatin and AmB

- Amphoteriin –B

  binds to ergostrol and disrupts fungal cell membrane

Initial test dose of 1 mg in 100ml of 5%d over 1 hr

Preloading - 500ml of saline

Amphotericin B dissolved in 500ml 5% dextrose and started at a small dose tranfused over 4-6hrs

dose increased in small increments to

0.3mg-1mg /kg

Dose concentration for infusion <0.1mg/ml

- Intrathecal administration

  initial dose-0.025mg

  gradually increased-0.25mg-0.5mg three times a week

Adverse effects-

  chills and rigors, hypotension

  Nephrotoxicity

  Thrombophlebitis

  Bone marrow suppression

  Electrolyte imbalances

Lipid formulations of polyenes

- Lipid formulations of polyenes
  - Improve the therapeutic index for polyene macrolides
  - AmB lipid complex
  - AmB colloidal dispersion
  - Liposomal AmB
    - invasive fungal infections in patients refractory or intolerant to standard AmB
  - Liposomal nystatin
    - phase III clinical trials

Lipid formulations of polyenes

- In vivo testing of liposomal AmB (1 or 3 mg/kg/d)
  - Significantly higher success rate than conventional AmB
  - Twofold to six fold decrease in drug-related adverse events
  - Lower incidence of severe drug-related side effects
  - Fewer nephrotoxicity

- Flucytosine

interferes with protein synthesis

dose- 100mg-150mg/kg/d

adverse effect- GI upset, hepatotoxic pancytopenia

- AZOLES

  interfere with ergosterol synthesis by binding to lanosterol 14-demethylase

  e.g.- voriconazole, fluconazole, itraconazole

Dose 200mg-1200mg/day

Adverse effect- nausea, loss of hair, gynecomastia, hepatotoxic

- Fluconazole given 400mg/d 8-12 weeks
- Itraconazole, ketaconazole- poor CSF penetration
- Voriconazole - 6 mg/kg IV Q12H for 1 day,
  4 mg/kg IV Q12H for 2weeks
  200mg oral 12hrly for 8-12 weeks
- Posaconazole salvage therapy for aspergillosis and candida

Anti fungal agents

Table 2: Likely intrinsic resistance to antifungal agents	
Amphotericn B	*Aspergillus terreus, Candida lusitaniae, Trichosporon beigelii, Scedosporium prolificans*
Flucytosine	Not to be used as single agent because of resistance.
	Molds, zygomycetes, dimorphic fungi, dematiaceous fungi, *Trichosporon beigelii*
Fluconazole	All molds, *Candida krusei*
Itraconazole	*Candida krusei*
Voriconazole	Zygomycetes, *Coccidioides immitis, Trichosporon* spp., *Fusarium* spp.
Echinocandins	Zygomycetes, *Cryptococcus neoformans, Trichosporon* spp., *Fusarium* spp.

- **New antifungal agents**
  - **Pradimicins-benanomicins**
    - **bind to cell wall mannoproteins causing osmotic sensitive lysis and cell death**
  - **Nikkonycins**
    - **competitive inhibitors of fungal chitin-synthase enzymes**
  - **Allylamines/thiocarbamates**
    - **non-competitive inhibitors of squalene epoxidase**
  - **Sordarins**
    - **inhibit protein synthesis, i.e. elongation factor 2**
  - **Cationic peptides**
    - **bind to ergosterol and cholesterol and lead to cell lysis**

Experimental immunotherapy

- Increase neutrophil , stimulate neutrophils and macrophages - G-CSFs and GM-CSFs
- Increase cellular immunity- IFN-gamma
- Increase humor immunity- vaccines

Literature review

- Intracranial fungal granuloma

  Prof B.S.Sharma etal Dept of neurosurgery PGI chandigarh. Surgical neurology1997,47:489-97

Thank you